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Invited Minireview

The influence of glucocorticoid signaling on tumor progression

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ABSTRACT

The diagnosis of cancer elicits a broad range of well-characterized stress-related biobehavioral responses. Recent studies also suggest that an individual's neuroendocrine stress response can influence tumor biology. One of the major physiological pathways altered by the response to unrelenting social stressors is the hypothalamic–pituitary–adrenal or HPA axis. Initially following acute stress exposure, an increased glucocorticoid response is observed; eventually, chronic stress exposure can lead to a blunting of the normal diurnal cortisol pattern. Interestingly, recent evidence also links high primary tumor glucocorticoid receptor expression (and associated increased glucocorticoid-mediated gene expression) to more rapid estrogen-independent breast cancer progression. Furthermore, animal models of human breast cancer suggest that glucocorticoids inhibit tumor cell apoptosis. These findings provide a conceptual basis for understanding the molecular mechanisms underlying the influence of the individual's stress response, and specifically glucocorticoid action, on breast cancer and other solid tumor biology. How this increased glucocorticoid signaling might contribute to cancer progression is the subject of this review.

1. Introduction

The human biobehavioral response to stressors includes physiological changes that are initiated through an individual's interaction with the social environment. In response to these environmental stressors, including social stressors, well-defined physiological changes occur at the organismal level. These changes can be buffered by social support networks, thereby mitigating the deleterious effects of the stress response. However, when life's stressors are unrelenting and social support or other resources (e.g. financial resources) are insufficient, neuroendocrine pathways can become deregulated. It is this deregulation of physiological pathways that underlies the mechanisms whereby psychosocial stressors are hypothesized to influence the biology of chronic disease.

Cardiovascular and immune-related diseases have long served as examples of the stress response-disease relationship (Black and Garbutt, 2002; Stojanovich and Marisavljevich, 2008). More recent studies have begun to explore connections between psychosocial factors and cancer biology. Indeed, recent clinical, epidemiological, and animal-based studies suggest there is a biobehavioral influence on tumor progression (Armaiz-Pena et al., 2009; Costanzo et al., 2011). However, evidence for the impact of psychosocial factors on cancer initiation (rather than progression) has been less consistent (Costanzo et al., 2011). Nevertheless, it is well-established that neuroendocrine hormones (e.g. glucocorticoids and noradrenaline) can and do influence cancer biology (Armaiz-Pena et al., 2009). Thus, the fact that significant stress exposure can lead to deregulation of the neuroendocrine axis has led to further investigation into the effects of psychosocial factors on cancer biology as outlined below.

There are several neuroendocrine cell signaling mechanisms, executed downstream of both the adrenal and sympathetic systems, which could contribute to cancer growth. Recent reviews have outlined some neuroendocrine–cancer relationships and have extensively outlined neuroendocrine influences on the immune system (Armaiz-Pena et al., 2009; Costanzo et al., 2011). The immune system has well-established and important roles in the progression of some cancer types (e.g. melanoma and renal cell carcinoma); however, its role in other cancers is less well understood. The overall impact of the immune system on cancer biology [reviewed in (Grivennikov et al., 2010)] and specifically, the social stress-induced modulation of immunity are reviewed extensively elsewhere (Armaiz-Pena et al., 2009; Costanzo et al., 2011).

This review instead focuses specifically on glucocorticoids (GCs), steroid hormones that are either secreted from the adrenal gland during exposure to acute and chronic stressors or administered pharmacologically to reduce inflammation, and the role of GC signaling in epithelial cancer biology. We discuss potential mechanisms through which endogenous GCs (cortisol in humans and corticosterone in rodents) may influence cancer progression. These data suggest that the routine pharmacological use of

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synthetic GCs in some cancer treatment may not be optimal. Furthermore, we explore how psychosocial mechanisms might intersect with both systemic and tumor microenvironmental GC action to increase tumor progression.

2. Stress signaling: cortisol and the glucocorticoid receptor

2.1. Cortisol

The active GC in humans, cortisol, is produced and secreted by the adrenal cortex. Cortisol release into the circulation has important systemic roles in modulating metabolic and immune processes; cortisol also elicits cell-type-specific effects, some of which are discussed in detail below. Release of cortisol from the adrenal gland is regulated by the hypothalamic–pituitary–adrenal (HPA) axis, a biological circuit capable of integrating human experience with physiological signaling. In the stress response, specific neurons within the hypothalamus secrete corticotrophin-releasing hormone (CRH). In turn, CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which subsequently acts on the adrenal cortex to promote cortisol release. A negative feedback loop completes the HPA circuit resulting in cortisol suppressing the production of CRH and ACTH through feedback to the hypothalamus and pituitary. The HPA axis is further linked to the Circadian clock thereby resulting in regulation of GC levels in a diurnal pattern (Chung et al., 2011).

The biological effects of cortisol are in part mediated by the average concentration of circulating cortisol over a certain time period; however, cortisol levels within specific tissues also play an important role in its cell- and tissue-specific effects (Draper and Stewart, 2005). Two isozymes are responsible for regulating local cortisol levels within specific tissues, 11β-Hydroxysteroid dehydrogenase (11β-HSD) type I, which converts inactive cortisone to active cortisol, and 11β-HSD type II, which is responsible for the reverse reaction that inactivates cortisol. Accurately measuring tissue and intracellular concentrations of human cortisol remains challenging. However, transgenic mice with adipose tissue-specific overexpression of the gene encoding 11β-HSDI exhibit increased local corticosterone production and develop the metabolic syndrome, clearly demonstrating that a tissue-specific (rather than systemic) increase in active GCs can dramatically affect whole animal physiology (Masuzaki et al., 2001).

2.2. The glucocorticoid receptor

The most important determinant of cortisol action is its cognate binding protein, the glucocorticoid receptor (GR), which is a member of the nuclear receptor family. The GR's primary action is as a ligand-dependent transcription factor regulating gene expression. Prior to cortisol binding, the GR is cytoplasmic, where it exists in a complex with heat-shock protein 90 (Hsp90) and several immunophilins (Lewis-Tuffin and Cidlowski, 2006). Ligand binding by GC results in dissociation of the GR-Hsp90 complex, GR homodimerization, and nuclear translocation of the dimer (Lewis-Tuffin and Cidlowski, 2006). Within the nucleus, the GR regulates the expression of target genes, either directly through interacting with glucocorticoid response elements (GREs) or indirectly through interacting with other transcription factors that in turn bind to DNA.

Through GR activation, cortisol regulates numerous biological processes including metabolism, behavior, growth and cellular apoptosis. As mentioned previously, the specific response to GR activation is often dependent on the target cell or tissue type. How a single hormone-receptor interaction can result in such divergent effects in different cell types is still under active investigation and is likely to involve multiple mechanisms. For example, the GR exists as multiple transcriptional and translational isoforms (Oakley and Cidlowski, 2011). In addition, isoforms of the GR are each subject to post-translational modifications including ubiquitination, SUMOylation, acetylation, and methylation that have been shown to modulate the stability and/or function of the receptor (Duma et al., 2006; Oakley and Cidlowski, 2011). The GR can also undergo ligand-dependent phosphorylation at several serine residues, events that regulate its transcriptional activity (Duma et al., 2006). Notably, in rats subjected to the chronic stressor of social isolation, phosphorylation of the GR in the brain may regulate GR's transcriptional activity independently of elevated serum corticosterone levels (Adzic et al., 2009). Thus, the diverse effects of glucocorticoids in particular cellular contexts are likely due to the presence and proportion of specific GR isoforms and their post-translational modifications, as well as to the concentration of active GCs (Oakley and Cidlowski, 2011).

3. Pharmacological glucocorticoids and the role of GR activation in cancer

The potential for divergent GR activity in different cell types is striking when comparing GC effects on lymphocytic malignancies versus epithelial cell-derived cancers. In the former case, synthetic GCs, such as dexamethasone (DEX), are routinely used to induce apoptotic cell death in malignant lymphoid cells (e.g. lymphoma). Conversely, in epithelial (i.e. "solid") tumors, several reports suggest that GCs have the opposite effect: GCs stimulate anti-apoptotic gene expression and antagonize the ability of cancer cytotoxics to effectively induce cell death (Zhang et al., 2007). Despite mounting evidence in tumor models suggesting GC-mediated antagonism of therapy-induced tumor cell apoptosis, GCs are routinely administered before, during, and after epithelial cell tumor-chemotherapy to mitigate nausea and allergic reactions. This section will provide a brief historical perspective, focusing on the relatively recent data suggesting GCs antagonize the effectiveness of cancer cytotoxic therapy and will then highlight studies that have begun to identify the molecular mechanisms through which GCs (either endogenous or pharmacologically administered) influence solid tumor biology. Finally, we will discuss data that suggest careful reconsideration of GC use in cancer patients and underscore the potential negative impact of increased endogenous stress-induced GCs on effective cancer treatment.

3.1. Laboratory studies and model systems

One of the earliest reports of the cell survival effect by GCs was observed in immortalized human mammary epithelial cells (Moran et al., 2000). Using serum-free media and specific growth factor supplementation, Moran et al. identified novel antiapoptotic pathways in the breast epithelial MCF10A cell line and its derivative line, MCF10A-Myc. When plated under serum-free conditions, both cell lines displayed high levels of cell death. Upon addition of the GC hydrocortisone, cells were protected from apoptosis independently of activating the antiapoptotic PI3-K and Akt signaling pathways (Moran et al., 2000). In an extension to this study, GR activation in a panel of several breast cancer cell lines protected from serum deprivation-induced apoptosis (Mikosz et al., 2001). GR activation was associated with the rapid induction of the serum and glucocorticoid-regulated kinase-1 (SGK1), a protein kinase encoded by a direct GR target gene. This induction of *SGK1* expression was required for much of the GR-mediated protection from cell death usually induced by serum withdrawal (Mikosz et al., 2001; Wu et al., 2004).

In concurrent studies, another group of investigators attempted to define mechanisms by which paclitaxel (an anti-mitotic chemotherapy) induces cell death and reported an interesting result: GCs also inhibit apoptosis induced by paclitaxel in breast, ovarian and cervical cancer cells (Huang et al., 2000). This observation allowed Huang and colleagues to identify a role for NF-Kappa-B activity in paclitaxel-mediated cytotoxicity, because GCs altered its activity.

For other investigators, however, the observed GC-mediated antagonism of paclitaxel was the first evidence suggesting that synthetic GCs (and potentially high levels of endogenous cortisol) could inhibit the effectiveness of chemotherapy treatment by blocking tumor cell death (Herr et al., 2003; Wu et al., 2004). Wu et al. investigated GC effects on both paclitaxel- and doxorubicin-induced apoptosis in breast cancer cell lines (Wu et al., 2004). Using MCF-7 and MDA-MB-231 breast cancer cell lines, DEX treatment resulted in the inhibition of apoptosis induced by either commonly used breast cancer chemotherapy. As part of this study, microarray analyses were performed to better understand the global GR-mediated gene expression changes associated with cell survival. In addition to *SGK1*, mitogen-activated protein kinase phosphatase-1 (*MKP1*/*DUSP1*) and *IκBα* (encoding a negative regulator of the NFκB transcription factor), were identified among the top genes upregulated by DEX treatment. As had been observed with *SGK1* during serum deprivation (Mikosz et al., 2001), anti-apoptotic effects of DEX in breast cancer cells treated with paclitaxel or doxorubicin required either *MKP1*/*DUSP1* or *SGK1* induction (Wu et al., 2004). Thus, *SGK1* and *MKP1*/*DUSP1* were identified as GR transcriptional target genes whose protein products have important roles in GC-mediated cancer cell survival.

The first *in vivo* report of pharmacologic doses of GCs antagonizing chemotherapy came from Herr and colleagues (Herr et al., 2003). In this study, the effect of DEX on cancer chemotherapy-mediated apoptosis in human lung and cervical carcinoma cells grown in tissue culture and as xenografted tumors was investigated. Compared to animals treated with cisplatin alone, strong antiapoptotic tumor cell effects were observed when DEX was added to the animals' drinking water. Analogous results were observed in cell culture and these effects were associated with the negative regulation of pro-apoptotic genes of the death receptor and the mitochondrial apoptosis pathways. When the apoptosis-initiating caspases, caspase-8 and caspase-9, were introduced into cells, DEX-induced apoptosis resistance was attenuated (Herr et al., 2003). More recently, Zhang et al. reported a remarkably comprehensive analysis of GC effects on the chemotherapeutic cytotoxicity index of a large number of solid tumor cells (Zhang et al., 2007). In this study, cells of human malignant solid tumors derived from surgical specimens or established cell lines were examined in cell culture or as tumor xenografts, using several cytotoxic treatments and several different GCs. GC-induced resistance toward cytotoxic therapy was observed in 89% of over 150 analyzed tumor samples. Chemotherapy resistance was common, irrespective of the specific cytotoxic treatment or GC used, and occurred in association with inhibition of apoptosis, and/or promotion of cell cycle progression (Zhang et al., 2007).

Taken together, these data provide strong evidence suggesting that exogenous GCs and subsequent tumor cell GR activation inhibit cancer cell death pathways to promote cell survival in the setting of cancer therapy. In epithelial cell cancers, GR activation and the ensuing gene induction (*SGK1*, *MKP1*, and *IκBα*) and gene repression (death receptors and mitochondrial apoptosis genes) appear to have principal roles in GC-induced therapy resistance (Wu et al., 2004; Herr et al., 2003). These effects observed in epithelial tumors contrast dramatically with the GC-mediated cell death observed in lymphoid malignancies. Although the mechanisms underlying the divergent actions of GCs on solid vs. lymphoid cancers are not yet known, it is likely that cell context-specific transcriptional networks exist.

3.2. Clinical studies

To date, no prospective analysis of patient samples has assessed the effect of synthetic GCs on the growth or chemotherapy sensitivity of solid tumors; however, several retrospective analyses suggest GC administration induces chemotherapy resistance in cancers of the breast and lung, and enhances the risk of skin cancer and perhaps lymphoma (Herr and Pfitzenmaier, 2006). Additionally, a correlative study evaluated anti-apoptotic gene expression in tumor samples from patients randomized to normal saline or DEX (Melhem et al., 2009). DEX administration to patients was associated with reproducible and rapid up-regulation of known GR target genes (*SGK1* and *MKP1*/*DUSP1*) that are associated with antagonizing chemotherapy-induced ovarian cancer cell apoptosis (Melhem et al., 2009). More recently, in a meta-analysis of primary breast tumor gene expression, high expression of the gene encoding the GR (*NR3C1*) was found to correlate with a significantly shorter relapse-free survival of patients with early stage estrogen receptor negative (ER−) tumors either treated or untreated with adjuvant chemotherapy (Pan et al., 2011). Interestingly, in ER+ breast cancer patients, a high level of primary tumor GR expression was instead associated with a better outcome relative to low GR expression (Pan et al., 2011). GR-mediated upregulation of estrogen sulfotransferase, an enzyme involved in estrogen deactivation (Gong et al., 2008), may help to explain why GR activity has differential effects on ER+ and ER− breast cancer. It is also possible that a more complex crosstalk exists between the GR and ER, although both these hypotheses have yet to be formally tested. In summary, mounting clinical evidence suggests that GR activation by GCs could induce therapy-resistance in specific subsets of solid tumors. Specifically, in breast cancer, GR expression appears to differentially influence patient outcome depending on whether or not ER is expressed. The current data identify a need for well-designed prospective clinical trials to determine the effect of GC administration on solid tumor progression and patient outcome.

4. Endogenous glucocorticoids, stress response, and cancer progression

"Transdisciplinary" approaches apply expertise in two or more disciplines to a complex problem (Gehlert et al., 2010). For example, both psychology and cancer biology disciplines were recently applied to develop animal models that allow for in-depth analyses of stress responsiveness and tumor biology (Williams et al., 2009). This approach is beginning to uncover the molecular underpinnings linking the psychosocial stress response to cancer. For example, female Sprague–Dawley rats have an inherited genetic predisposition for spontaneous mammary tumor formation; McClintock and colleagues reported altered systemic GC regulation following exposure to the chronic stress of social isolation that was associated with a significantly increased mammary tumor burden (Hermes et al., 2009). In a related study, the transgenic SV40 T-antigen mouse mammary tumor model found that social isolation was associated with abnormal GC regulation in response to a superimposed acute stressor and also associated with increased mammary tumor growth (Williams et al., 2009). More recently, a human breast cancer xenograft model demonstrated that chemotherapy efficacy is significantly improved with concurrent transient systemic inhibition of the GR using the GR antagonist mifepristone (Skor and Conzen, unpublished data). In addition to supporting the hypothesis that psychosocial stressors contribute

to increased tumor growth through GR signaling, these *in vivo* studies also suggest that altered endogenous GC activity plays a mechanistic role linking stress to cancer biology. Additional animal models have observed effects of altering the social environment on cancer growth (Cao et al., 2010). Future studies focusing on genetic and pharmacologic manipulation of specific neuroendocrine components will help tease out the most influential neuroendocrine effectors for specific cancers.

In cancer patients, alterations in cortisol regulation have been observed. For example, women with metastatic breast cancer frequently have flatter than normal diurnal cortisol patterns, and the degree of diurnal variation may predict earlier breast cancer mortality (Sephton et al., 2000). While the flattened cortisol levels in metastatic patients might be related to tumor burden, the diagnosis of cancer can also elicit a broad range of patient-specific psychological stress-related responses. For example, a recent study reported that some recently diagnosed breast cancer patients with avoidant coping mechanisms also had flattened diurnal cortisol rhythms (Dedert et al., 2012). Whether altered cortisol regulation plays a direct role in human tumor progression at the cellular level has yet to be determined; however, available laboratory evidence cited above suggesting a role for GR signaling in cancer supports the importance of evaluating the psychological stress response and tumor recurrence.

Based on the hypothesis that an intervention that reduces the stress response might also lower GC levels and slow tumor growth by preventing cancer cell survival pathways, a more recently reported prospective clinical trial evaluated the effect of supportive-expressive group therapy (SEGT) on survival of patients with metastatic breast cancer. Researchers found no effect in patients with ER+ breast cancers, but a positive effect of therapy on reducing tumor progression within the subset of patients with ER− breast cancer (Spiegel et al., 2007). However, another randomized trial of SEGT plus relaxation therapy versus relaxation therapy alone found that patient survival was not prolonged with the addition of SEGT, regardless of tumor ER status (Kissane et al., 2007). More recently, Andersen and colleagues reported a prospective clinical trial in which patients with recently treated early stage breast cancer were randomized to psychological intervention plus assessment or assessment-only cohorts (Andersen et al., 2008). Patients in the intervention arm had a reduced risk of both recurrence and breast cancer-related death. Interestingly, patients with cancer recurrence exhibited higher cortisol levels 17 months prior to relapse compared to patients that remained disease free (Andersen et al., 2008). Clearly, the impact of effective intervention to significantly reduce the psychological stress response in breast cancer patients requires further investigation with careful analysis of breast cancer subtype and diurnal cortisol levels.

5. Cancer-promoting effects of GCs in the tumor microenvironment

GC-mediated mechanisms influencing solid tumor progression are not limited to the effects of GCs directly on tumor cells. Tumor progression involves simultaneous interactions between the cancer cell, the microenvironment that supports the cancer cell's proliferation, the host and the individual's environment (Fig. 1). Neuroendocrine pathways have diverse targets. Indeed, nearly every mammalian tissue is believed to express the GR. Thus, attempting to integrate stress physiology with aspects of cancer progression also requires examining the tumor-microenvironment and an individual's systemic physiology to fully understand how the stress response influences tumor progression.

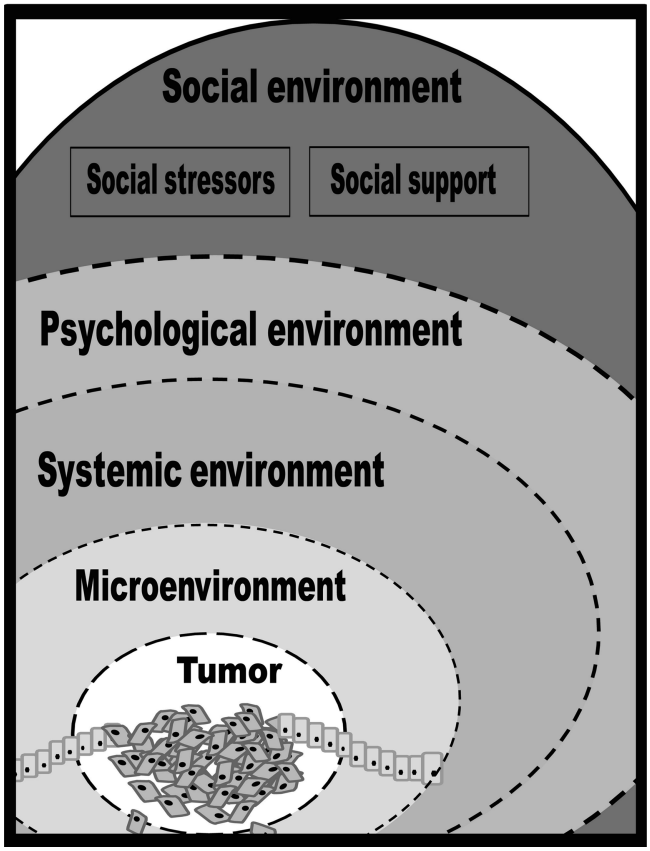

Fig. 1. The multi-layered environments of tumor growth within an individual. The malignant cell environment exists within a nested series of environments capable of varying levels of reciprocal communication. The stressors and support systems of an individual's social environment (dark gray) can interact with an individuals psychological environment (dark pink) to impact the physiology of the systemic environment (pale gray). These physiological changes can promote tumor progression by directly affecting tumor biology or indirectly though the microenvironment (pale pink). Transdisciplinary research considers all five environments through the coordinated experiments of both social and biological scientists using unifying model systems.

5.1. GCs in the tumor microenvironment

Genetic alterations can result in the uncontrolled growth and proliferation of otherwise normal cells. Given the proper time and conditions, cells lacking normal growth and proliferative controls can progress to become cancerous lesions. However, tumor progression is only partially dependent on cell-autonomous programming. Signals extrinsic to the tumor cell, including circulating systemic neuroendocrine and paracrine factors as well as those factors derived from cells in close proximity to the tumor cells (e.g. stromal cells), can influence overall tumor growth dramatically [reviewed in (Liotta and Kohn, 2001)]. Indeed, stromal signals from cells in the tumor microenvironment are increasingly appreciated as significant factors influencing tumor progression. Importantly, the tumor-stroma "crosstalk" is not unidirectional, but instead a dialogue involving enzymes, metabolites, growth factors and other cytokines on both compartments. Notably, both cancer cells and stromal cells can express the GR and are therefore likely influenced by variations in GC signaling.

The GR is expressed to varying degrees in almost every cell in the body. This includes the most commonly studied stromal constituents: fibroblasts, macrophages, adipocytes and immune cells. Developing systems that allow for accurate measurement and identification of relevant tumor-stroma interactions continues to

be challenging. However, gene expression profiling studies have compared tumor-associated stroma to normal stroma and suggest that cancerous cells can dramatically alter stromal mRNA expression (Finak et al., 2008; Smith et al., 2007). Using semi-quantitative PCR, Smith and colleagues analyzed mammary gland stromal mRNA expression of several nuclear receptors, including the GR (Smith et al., 2007). Significant differences in expression between cancer-associated stroma and control tissues were seen for the GR and the progesterone receptor (PR). GR showed increased expression in the stroma from later stage patient samples, whereas PR was decreased in expression compared to control stroma (Smith et al., 2007). Although this study was correlative and did not determine how or if increased GR expression contributed to tumor progression, it does suggest that GC signaling in the tumor microenvironment could be altered by paracrine- or endocrine-associated upregulation of GR expression.

The specific cells of the tumor microenvironment that display altered tumor-promoting signals in response to GCs have yet to be determined. The immune cell-modulating effects of GCs within the cancer microenvironment are one example whereby GCs could affect stromal cell populations. Notably, cancer-associated fibroblasts, which have established roles in cancer growth, invasion and migration, have been reported to have altered GR-mediated transcriptional activity (Hidalgo et al., 2011). Additionally, increased GCs can induce insulin resistance in adipocytes, a major component of the mammary microenvironment. Insulin-resistant adipocytes secrete pro-inflammatory cytokines and growth factors, many of which have been implicated in tumor progression (Park et al., 2011). Adipocytes also express high levels of 11β-HSD1, the enzyme responsible for generating active GC from its inactive precursor, and could influence GR tumor signaling through upregulating local GC levels (Masuzaki et al., 2001). Although indirect (e.g. stroma-mediated) influences by GCs on tumor progression are likely, much work remains to be done to better delineate how the tumor microenvironment is affected by increased GR signaling.

5.2. Systemic cancer-promoting effects of GCs

Systemic GCs can also influence tumor progression indirectly through their effects on the immune system and sytemic metabolism. Because of the role of the stress response in immune-modulation and GC-induced apoptosis of lymphoid-derived tumor cells, much of the biobehavioral research linked to cancer biology has focused on immune system function (Armaiz-Pena et al., 2009; Costanzo et al., 2011). Contrary to GC's role in immune function, GC-mediated metabolic modulation in relation to cancer biology is much less studied. However, strong associations exist between metabolic disorders, such as obesity and the metabolic syndrome, and the increased incidence and natural history of several types of cancer (Kaidar-Person et al., 2011). The underlying mechanisms establishing these links are unclear; however, elevated serum glucose and insulin levels, abnormal lipid profiles, and systemic inflammation are examples of likely mechanisms linking altered metabolism to cancer biology. Indeed, the high-energy demand of rapidly proliferating cancer cells is in line with increased energy substrates and growth factor availability of various metabolic disorders that facilitate pro-tumorigenic effects. Notably, neuroendocrine stress pathways and metabolic pathways are known to have important overlap. Indeed, GCs have potent effects on all of these potential metabolic links to cancer. Elevations in GCs can cause adipocytes, predominantly in visceral fat depots, to favor energy storage (Masuzaki et al., 2001) and accumulation of visceral fat has deleterious effects on systemic metabolism. For example, the best predictor of adverse consequences associated with obesity is the amount of visceral fat rather than total body fat mass (Masuzaki et al., 2001).

The effects of elevated GCs on adipose tissue accumulation also involve interactions within the CNS. Animal models suggest that during stressful experiences increased circulating GCs and insulin increase the drive for calorically dense foods (Dallman et al., 2005). Interestingly, consumption of calorically dense foods seems to attenuate the overall stress response, leading some investigators to conclude that increased consumption of high-calorie "comfort" food is a physiological means to cope with unrelenting stressors (Finger et al., 2011). In man, dietary changes are a common behavior seen in those individuals responding to overwhelming stressors (Wallis and Hetherington, 2009). However, some individuals consume more calories under stress, while others eat less. In those individuals who consume more food, GC action in peripheral tissues (i.e. visceral adipose tissue) and GC action in the CNS may act in a feed forward loop to promote weight gain (Pecoraro et al., 2004). Chronic stressors and the ensuing alterations in endogenous GC secretion are associated with behavioral changes that can disrupt whole-body metabolism. Through exacerbating the onset of obesity, the metabolic syndrome, and the associated hyperglycemia and hyperinsulinemia, increased endogenous GCs, secondary to the biobehavioral stress response, might also provide indirect mechanisms to facilitate cancer growth.

5.3. Closing remarks

Cancer patients diagnosed with solid tumors face emotional and social stressors that can be associated with significantly disrupted endogenous cortisol production. Furthermore, pharmacologic GC therapy is frequently administered to cancer patients to reduce the associated side effects of chemotherapy. The extent to which endogenous and synthetic GCs overlap and influence epithelial cancer biology remains poorly understood; however, recent evidence suggests that both may promote tumor growth. Anti-apoptotic mechanisms in tumor cells may be important determinants of synthetic GC-mediated chemotherapy resistance, although high endogenous GCs also likely initiate increased GR-mediated anti-apoptotic signals in malignant epithelial cells. In addition, even prior to a cancer diagnosis, deregulated endogenous GC signaling that occurs during exposure to unrelenting stressors may have important direct effects on promoting pre-malignant tumor growth and on the tumor microenvironment. Finally, associated metabolic alterations following exposure to unrelenting social stressors could synergize with GC deregulation to generate a pro-tumorigenic host environment.

Much work is still needed to determine the mechanisms through which GCs influence tumor progression in specific tumor cell types. There is also a need for prospective clinical trials to evaluate the effect, if any, of administering synthetic GCs on patient outcome. Exposure to unrelenting stressors and the resulting alteration in GC levels in cancer patients may also contribute to tumor growth, suggesting the importance of identifying such patients for intervention. The recently reported benefits in subsets of cancer patients randomized to psychosocial-intervention suggest that modulating the neuroendocrine stress response deserves further investigation. In addition to psychosocial and behavioral intervention, targeting the neuroendocrine effector pathways in tumors cells (e.g. the use of GR antagonists and GR selective modulators) may benefit those cancer patients with specific tumor cell or tumor microenvironment characteristics make them particularly susceptible to GC signaling effects – for example tumors demonstrating relative overexpression of the GR. In summary, understanding the influence of glucocorticoid signaling in human cancer biology will require coordinated efforts from both the cancer and behavioral researchers whose common goal is to optimize patient care.

Conflict of Interest

Dr. Conzen has a patent application pending proposing the use of glucocorticoid receptor antagonism in breast cancer. There is no financial conflict of interest.

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